objected to because the Examiner contends that independent claims 36 and 37 are drawn to a tissue collection medium rather than a tissue collection medium comprising cells or tissue.

Response to 35 U.S.C. §103 Rejections

1. Claims 36-48, 51-54, 58, 59 and 61 have been rejected under 35 U.S.C. § 103(a) for being unpatentable over Dunphy U.S. Patent No. 5,679,333. Applicants respectfully disagree with this rejection. The Examiner states that Example 4 of Dunphy discloses a medium for fixing tissue for histological procedures, and that it would be obvious to modify this medium with EDTA.

The claimed invention pertains to a cell or tissue collection medium and a method of cell sample collection, wherein the cells or tissue contained in the medium can be analyzed directly by both cytological and molecular methods, and wherein the molecular method of analysis comprises either RNA or DNA or protein analysis. In view of the attached Declaration under 37 C.F.R. §1.132, applicants show that Dunphy's Example 4 formulation is not capable of adequately preserving DNA and RNA for molecular analysis.

The Declaration is based on a set of experiments comparing Dunphy's Example 4 formulation with a 'UCM' formulation in their ability to preserve nucleic acids for molecular analysis. As described in paragraph no. 10 of the Declaration, the direct analysis of nucleic acids was conducted by following the method for detecting DNA and RNA by the Digene Hybrid Capture (HC) method. This method revolves around the hybridization of either an RNA probe for DNA targets or a DNA probe for RNA targets. Specific detection of RNA or DNA targets is contingent upon an antibody that binds to DNA-RNA hybrids. Thus, if the DNA or RNA target in a particular cell/tissue collection medium is not degraded, then a probe will be able to

hybridize to its target for subsequent detection by an anti-DNA/RNA hybrid antibody and chemiluminescence.

As shown in Tables 1 and 2 of the Declaration, none of the Dunphy Example 4-based formulations are capable of preserving DNA. By week 3, the UCM formulation maintained 97% (Table 1) and 99% (Table 2) of its initial signal, whereas the Dunphy Example 4 formulations only maintained 12-18% (Table 1) and 9-15% (Table 2) of their initial signal.

As shown in Tables 3 and 4 of the Declaration, none of the Dunphy Example 4-based formulations are capable of preserving RNA. By day 14, the UCM formulation maintained 94% (Table 3) and 95% (Table 4) of its initial signal, whereas the Dunphy Example 4 formulations only maintained 2-7% (Table 3) and 9-14% (Table 4) of their initial signal.

In paragraph no. 24 of the Declaration, Dr. Attila Lorincz states the addition of EDTA to the Dunphy Example 4 formulations will not improve RNA stability. Dr. Lorincz points out that EDTA is not considered to be a general ribonuclease inhibitor. Thus, the addition of EDTA to Dunphy's Example 4 formulation will not rectify this formulation's inability to preserve RNA, and therefore the addition of EDTA to Dunphy's Example 4 formulation does not make obvious the claimed medium which allows the direct molecular analysis of RNA.

Lastly, the Examiner contends that because Dunphy's Example 4 formulation contains the same basic elements as the claimed formulations, the Examiner therefore considers that Dunphy's Example 4 formulation makes obvious a cell/tissue preservation medium allowing the direct molecular analyses of nucleic acids. But the Declaration shows there is an extreme difference between the UCM's and Dunphy's Example 4 ability to preserve nucleic acids for molecular analysis. Thus, applicants assert that the claimed UCM formulation provides surprising, unexpected and superior results which have a significance greater than the expected

properties of the claimed medium. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties...can be enough to rebut a prima facie case of obviousness" (In re Chupp, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)). Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

2. Claims 49, 55-57, 60, and 68-74 have been rejected under 35 U.S.C. § 103(a) for being unpatentable over Dunphy, U.S. Patent No. 5,679,333, in view of Weber, International Publication No. WO 94/02645, further in view of Harrison, U.S. Patent No. 4,578,282. The Examiner contends that Dunphy as applied to Weber and Harrison makes it obvious to use tissue samples treated with the collection medium of Dunphy for methods of DNA and protein analysis, as Weber shows that such media can be used for DNA hybridization studies and Harrison shows that such media may be used for antigen analysis. Applicants respectfully disagree with this rejection.

As stated above, Dunphy's Example 4 formulation does not adequately preserve nucleic acids for direct molecular analysis. Neither Weber nor Harrison remedies this defect. Weber's preferred hybridization solution contains:

> In a preferred embodiment, the hybridization solution of the one-step *in situ* method consists of 25% formamide, 5X SSC, 15X Ficoll/PVP, .4 M guanidinium isothiocyanate, about 50 mM sodium phosphate (pH 7.4), 50 mM DTT, about 1 mg/ml salmon sperm DNA, 5% Triton X-100, 50 mM EDTA and 21% PEG. (page 16, lines 16-19)

However, there is no teaching or suggestion within Weber to instruct one skilled in the art to modify this medium in relation to Dunphy's Example 4 formulation such that the combination would result in a formulation that allows the direct molecular analysis of nucleic acids and

proteins. Further, there is no reasonable expectation that any such combination would succeed in forming a medium as claimed.

As for the Harrison patent, this reference does not even describe a collection medium. Harrison describes, "a fixative which is pre-applied to a slide or other test surface and which presents a substantially dry, non-fluid surface to which the sample is applied." (column 1, lines 41-45). Thus, Harrison describes a dry fixation process for antigen analysis. One skilled in the art could not reach the instant method claims based on the teachings of Dunphy in combination with Harrison. Further, Dunphy in combination with Harrison and Weber still do not lead the skilled artisan to a useful formulation as claimed, because neither Dunphy nor Harrison nor Weber provide a specific formulation capable of preventing degradation of nucleic acids and proteins. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

3. Claims 62-66 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Dunphy U.S. Patent No. 5,679,333 in view of Wainwright U.S. Patent No. 5,370,128. The Examiner contends that Wainwright discloses an article of manufacture comprising a container, a lid fitting the container and a brush for preserving a cell sample. Applicants respectfully disagree with this ground of rejection.

As discussed above, Dunphy fails to teach or suggest the claimed invention because it does not teach a tissue/cell preservation medium that is capable of preserving nucleic acids for direct molecular analysis. Wainwright does not remedy the defect of Dunphy, but rather merely describes a container with a lid and a brush. Wainwright only refers to a fixative once, "Inside the container is 2 CCs of cytofixative to preserve the specimen." (column 5, lines

43-44). Wainwright does not disclose what this cytofixative may be composed of, nor does Wainwright disclose that this cytofixative may enable the fixation of cells for molecular analysis. Therefore, the combination of Wainwright with Dunphy does not rectify the inability of Dunphy's medium to adequately preserve nucleic acids for direct molecular analysis. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

4. Claim 67 has been rejected under 35 U.S.C. § 103(a) for being unpatentable over Dunphy, in view of Wainwright, further in view of Weber, in view of Harrison. The Examiner contends that this combination is warranted because Weber and Harrison respectively show that aldehydes, such as formaldehyde or glutaraldehyde, are useful cross-linking agents in tissue collection media.

As presented previously, neither Wainwright, Weber nor Harrison teach or suggest a remedy for the defects in Dunphy's Example 4 formulation. Applicants assert that there is no guidance in this combination of references to provide a successful medium composition capable of adequately preserving cells or tissues for the direct molecular analysis of nucleic acids and proteins. The combination of Weber and Harrison is improper because Weber discloses the use of proteolytic and denaturing agents (such as proteinase K and guanidine isothiocyanate) that would not enable the further analysis of proteins. Harrison, as discussed above, describes the use of a dry fixative process, and therefore provides no teaching or suggestion for a tissue preservation medium. Lastly, Wainwright makes no suggestion or teaching that its article of manufacture may be used to collect cells for protein or nucleic acid analysis; rather Wainwright only directs one skilled in the art that the invention is useful for the cytologist in analyzing pap smears. Thus, applicants respectfully disagree with the combination

of Dunphy, Wainwright, Weber and Harrison because the combination is improper and because the combination does not remedy the defects in the primary reference. Therefore, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Response to Double Patenting Rejection

Claims 36-74 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 29-41, 46-55, 60-66, 71-75, and 80 of copending application Serial No. 09/598,571, in view of Weber, in view of Harrison. Applicants respectfully disagree with the combination of the co-pending application with Weber and Harrison. Applicants provisionally agree to file a terminal disclaimer in one of the applications upon issuance of claims in the other application. The filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991). Applicants respectfully request reconsideration and withdrawal of the double patenting rejection.

AUTHORIZATION

No additional fee is believed necessary. However, the Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2629-4005US1.

Respectfully submitted,

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APPENDIX

36. (Amended) A cell or tissue collection medium, [wherein the] allowing both cytological and molecular methods of analysis of cells or tissues collected [in the medium] therein, [can be analyzed directly by both cytological and molecular methods] wherein the molecular method of analysis comprises either RNA or DNA or protein analysis or the analysis of both RNA and DNA, and wherein the medium is water based and comprises an alcohol, a cross-linking agent and an anti-degradation agent, and wherein the cross-linking agent is an aldehyde comprising about 1% to about 15% of the medium.

37. (Amended) A cell or tissue collection medium, [wherein the] allowing both cytological and molecular methods of analysis of cells or tissues collected [in the medium] therein, [can be analyzed directly by both cytological and molecular methods] wherein the molecular method of analysis comprises either RNA or DNA or protein analysis or the analysis of both RNA and DNA, and wherein the medium is water based and comprises an alcohol, a cross-linking agent and an anti-degradation agent, and wherein the cross-linking agent is an aldehyde comprising about 1% to about 10% of the medium.

AUTHORIZATION

No additional fee is believed necessary. However, the Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2629-4005US1.

Respectfully submitted,

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